A STUDY OF RENAL DYSFUNCTION IN COPD PATIENTS

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CHENNAI

APRIL - 2013

CERTIFICATE

This is to certify that this dissertation titled

"A STUDY OF RENAL DYSFUNCTION IN COPD PATIENTS"

is the bonafide work done by **Dr. IDHAYA CHANDRAN.N,** Post Graduate Student (2010 – 2013) in the Department of General Medicine, Govt. Stanley Medical College and Hospital, Chennai under the direct guidance and supervision and in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R. Medical University, Chennai for M.D. Branch I, General Medicine Degree Examination to be held in April 2013.

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I, **Dr. IDHAYA CHANDRAN.N.,** solemnly declare that the dissertation titled

"A STUDY OF RENAL DYSFUNCTION IN COPD PATIENTS"

is a bonafide work done by me at Govt. Stanley Medical College and Hospital from May 2010 to Oct 2012 under the guidance and supervision of my unit chief,

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Dr. Idhaya chandran. N

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LIST OF ABBREVIATIONS

COPD	Chronic Obstructive Pulmonary Disease.
CRF	Chronic Renal Failure.
FEV_1	Forced Expiratory Volume in 1 second.
FVC	Forced Vital Capacity.
GFR	Glomerular Filtration Rate.
RPF	Renal Plasma Flow.
MDRD	Modification of Diet in Renal Disease.
NKF	National Kidney Foundation.
KDOQIG	Kidney Diseases Outcome Quality Initiative Guidelines.
PRA	Plasma Renin Activity.
RAS	Renin Angiotensin System
AT II	Angiotensin II
AVP	Arginine Vasopressin

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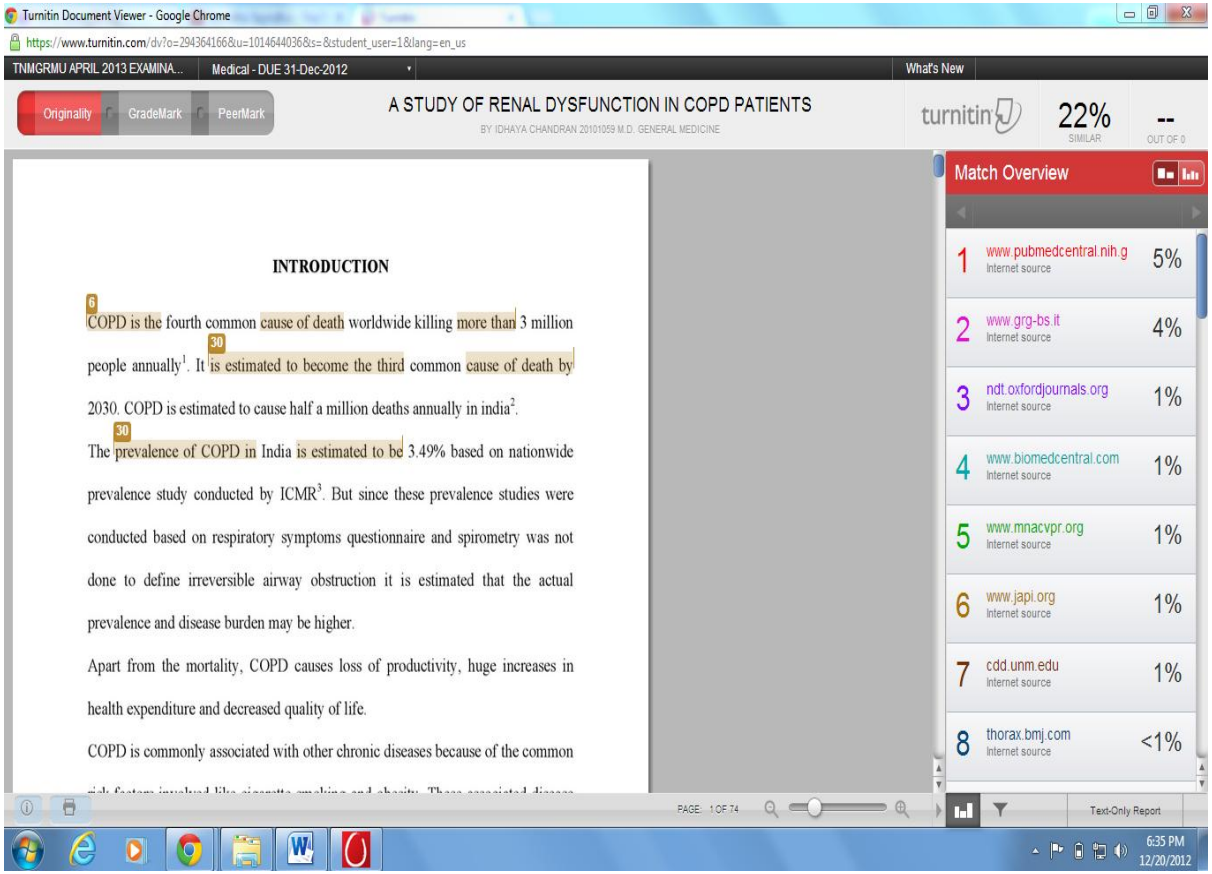
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The 30 prevalence of COPD in India is estimated to be 3.49% based on nationwide prevalence study conducted by ICMR[3]. But since these prevalence studies were conducted based on respiratory symptoms questionnaire and spirometry was not done to define irreversible airway obstruction it is estimated that the actual prevalence and disease burden may be higher.
Apart from the mortality, COPD causes loss of productivity, huge increases in health expenditure and decreased quality of life.
COPD is commonly associated with other chronic diseases because of the common
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INTRODUCTION

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COPD is commonly associated with other chronic diseases because of the common risk factors involved like cigarette smoking and obesity. These associated disease conditions might contribute significantly to the symptoms and severity in the affected patients. The diseases associated with COPD include congestive heart failure, arrhythmias, peripheral artery disease, coronary artery disease, diabetes, hypertension, osteoporosis, cachexia, chronic renal failure, infections and lung cancer. It is important to screen COPD patients for

the associated comorbid illness since addressing these associated illness can lead to better patient management.

The prevalence of chronic renal failure increases with age. Chronic renal failure is associated with many chronic diseases such as diabetes, hypertension, and congestive heart failure. The association of chronic renal failure with COPD has been recognized only recently. This might have therapeutic implications like modification of dose of drugs excreted by kidneys. Understanding the pathogenesis of renal failure in COPD can lead to novel treatment strategies in the management of COPD in future.

The association of chronic renal failure with COPD has been demonstrated in western population. This association has not been studied in our patients. Hence we took up the study to find the association of renal failure in COPD patients and its significance.

REVIEW OF LITERATURE

Chronic obstructive pulmonary disease (COPD) is a preventable disease characterized by expiratory airflow limitation which is usually progressive .The disease is due to an abnormal inflammatory response of the lung to noxious particles or gases, in almost all patients due to cigarette smoking. In many patients it could be due to exposure to pollutants and noxious gases due to cooking with biomass fuels especially in developing countries and this could explain disease in nonsmokers[4]. Chronic bronchitis and emphysema are two conditions found commonly associated with COPD.

EMPHYSEMA:

Emphysema can be defined pathologically as the enlargement of distal airways due to destruction of acinus and disappearance of alveolar septae. This results in characteristic loss of elastic recoil which in turn causes slowing of airflow from the lungs, hyperinflation, and air-trapping.

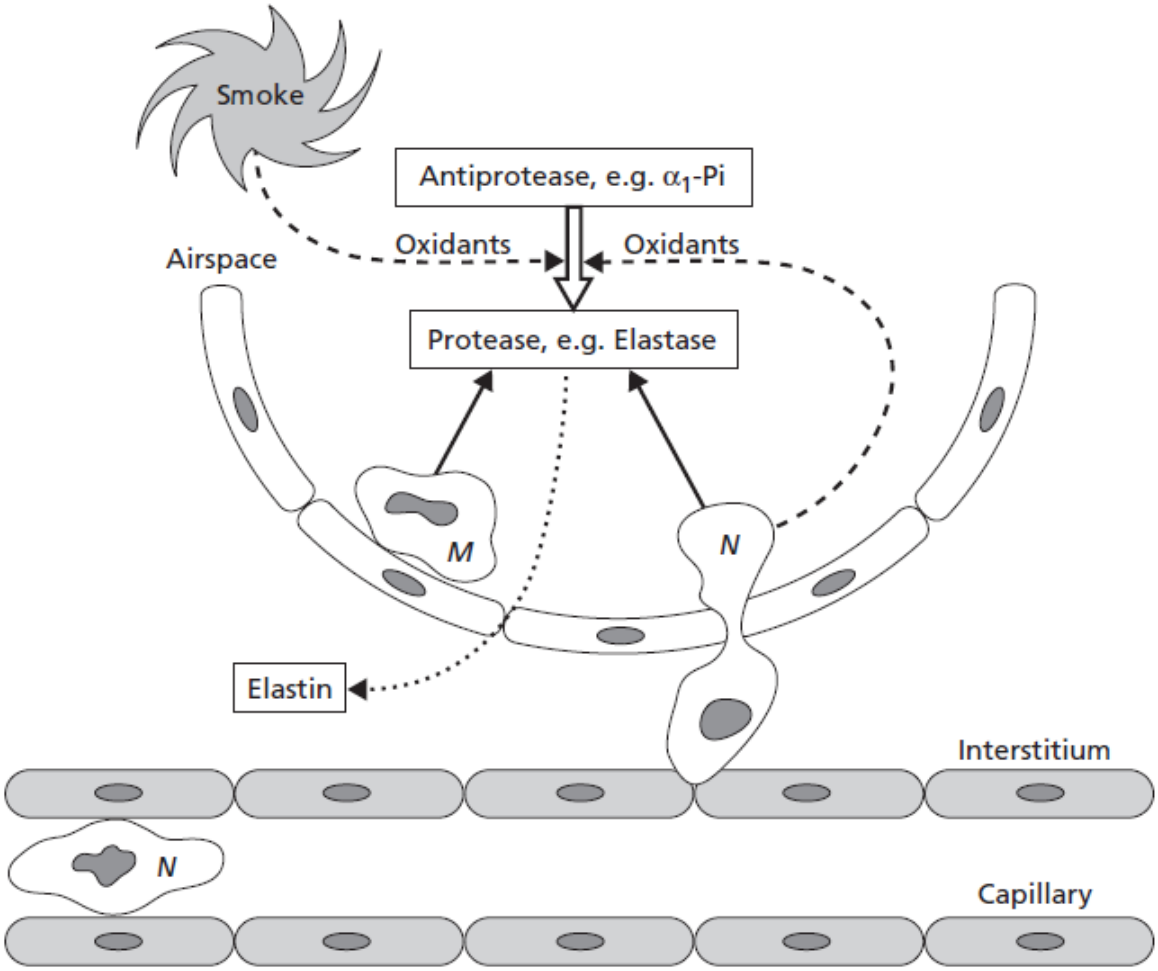


FIGURE 1: PATHOGENESIS OF EMPHYSEMA

CHRONIC BRONCHITIS

Chronic bronchitis is characterized by chronic cough and sputum production, which is present in about one out of three people with early COPD. It is defined as productive cough on most days of the month for at least 3 consecutive months per year for at least 2 consecutive years.

Chronic cough and sputum production in cigarette smokers may not be associated with chronic airflow obstruction. *Chronic obstructive bronchitis* defines chronic mucus hypersecretion associated with airflow obstruction. The anatomic correlates of chronic bronchitis are mucus gland hyperplasia and goblet cell metaplasia in large and medium-size airways. Patients with COPD can also have inflammation, narrowing, tortuosity and fibrosis of the *small and medium-size airway* that contributes to the airflow limitation.

Some long-standing asthmatics develop airflow obstruction that is not completely reversible, episodes of cough and wheeze, and chronic sputum production. These individuals are said to have *chronic asthmatic bronchitis* and tend to have a somewhat better prognosis for survival than those with typical COPD associated with cigarette smoking. It is difficult to distinguish between these two subgroup of patients.

DIAGNOSIS:

Physical examination and chest imaging are insensitive methods for diagnosis of COPD. Physical findings of hyperinflated lungs such as low-lying diaphragms, decreased breath sounds and hyperresonant chest percussion are highly specific for COPD, but usually only in advanced disease. It has been suggested in a study that a distance between the thyroid cartilage and the sternal notch less than 4 cm in a smoker older than age 45 is highly indicative of the presence of COPD. Clubbing of the fingers is not common in COPD and, if

present, suggests another diagnosis such as bronchiectasis, asbestosis, or lung cancer.

High-resolution computed tomography (HRCT) of the lung, analyzed by quantitative measures of lung density, is a promising technique for early detection of emphysema, but the role of HRCT in early detection and monitoring of COPD is not established at present.

α1-Antitrypsin deficiency is an uncommon, but not rare, condition associated with premature emphysema. Testing for α1-antitrypsin deficiency is indicated in patients with premature disease.

HIV/AIDS is also associated with premature emphysema, and screening for HIV should be considered in persons with emphysema and HIV risk factors such as intravenous drug use or high-risk sexual activity.

SPIROMETRY

The spirometry is a simple, noninvasive, and inexpensive test used in the diagnosis of COPD. Spirometry is also used in the classification of its severity and monitoring the progression of the disease. The FEV1/FVC ratio reflecting the rate of emptying of the lung is used to define the presence of an obstructive ventilatory defect. A ratio less than 0.70 is used to define COPD. Once airflow obstruction is established, the severity of the disease is classified by the reduction of FEV1 compared with a healthy reference population.

STAGE		CHARACTERISTICS
I	MILD COPD	FEV1 80% predicted
II	MODERATE COPD	FEV1 50%–79% predicted
III	SEVERE COPD	FEV1 30% to 49% predicted
IV	VERY SEVERE COPD	FEV1 <30% predicted or <50%predicted with room air PaO2 <60 mm Hg (8.0 kPa)

TABLE 1: CLASSIFICATION OF COPD SEVERITY[5]

CONDITIONS SUGGESTING ALPHA 1 ANTI- TRYPSIN DEFICIENCY[6]

1. Early-onset emphysema (age under 45 years).
2. Emphysema in a nonsmoker.
3. Emphysema predominantly in lung bases (pan-acinar).
4. Necrotizing panniculitis (Weber-Christian disease).
5. C-ANCA positive vasculitis (e.g.,Wegener's granulomatosis).
6. Family history of early onset emphysema or non-smoking–related emphysema.
7. Bronchiectasis without other etiology.

PROGNOSIS

The median survival after the diagnosis of COPD is 10 years. But the disease has one of widely varying rates of progression. Death is often due to susceptibility to intercurrent illness and other smoking related illness such as lung cancer rather than progressive respiratory failure.

The factors that have been identified to predict poor survival in COPD include low FEV1, active smoking status, hypoxemia, poor nutrition, the presence of cor pulmonale, resting tachycardia, low exercise capacity, severe dyspnea, poor health-related quality of life, anemia, frequent exacerbations, co-morbid illnesses, and low carbon monoxide diffusing capacity.

Patients with an FEV1 less than 35 percent predicted have about 10 percent mortality per year. If a patient reports that they are unable to walk 100 meters without stopping because of breathlessness, the 5-year survival is only 30 percent.

BODE INDEX [7]

A multidimensional prognostic index that takes into account several indicators of COPD prognosis is the BODE index (*b*ody mass index [BMI], *o*bstructive ventilator defect severity, *d*yspnea severity, and *e*xercise capacity). The components are derived from

1. Body mass index (weight in kg/ square of height in m).
2. FEV1 percent predicted.
3. Modified Medical Research Council (MMRC) dyspnea score.
4. Distance walked in 6 minutes in meters.

A BODE score greater than 7 is associated with a 30 percent 2-year mortality; whereas a score of 5 to 6 is associated with 15 percent 2-year mortality. If the BODE score is less than 5, the 2-year mortality is less than 10 percent.

VARIABLE	**0**	**1**	**2**	**3**
FEV1 (% predicted)	≥65	50 – 64	36 – 49	≤35
Distance walked in 6 min (meters)	≥350	250 – 349	150 – 249	≤149
MMRC dyspnea scale	0 – 1	2	3	4
Body-mass index (kg/M2)	<21	≥21		

TABLE 2: CALCULATION OF BODE INDEX

GRADE	DESCRIPTION
0	Not troubled with breathlessness except with strenuous exercise.
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level.
3	Stops for breath after walking about 100 yards or after a few minutes on the level.
4	Too breathless to leave the house or breathless when dressing or undressing.

TABLE 3: MODIFIED MEDICAL RESEARCH COUNCIL DYSPNOEA (MMRC) [8] SCALE

MANAGEMENT OF COPD

SMOKING CESSATION

In patients who continue to smoke cigarettes there are no proven treatments that prevent the progression of COPD. C*essation of smoking* halts the excessive decline in lung function. Hence efforts directed to stop smoking should be a primary goal for physicians caring for COPD patients. Patients with mild or moderate COPD who are asymptomatic might be unaware of the fact

that they have underlying lung disease that can be halted by smoking cessation or may adopt a fatalistic attitude that it is too late for help.

Even patients with severe disease who are dyspneic at rest or use continuous oxygen may continue to smoke cigarettes or relapse after quitting. At each patient encounter smoking history should be obtained because many patients do not volunteer the extent of their smoking or report a smoking relapse following cessation. In patients who do smoke, achieving cessation should be a primary and persistent goal of treatment.

The counseling by the physician should emphasize the harm of continued smoking, the benefits of cessation in terms of activities that are meaningful for the individual and the understanding that smoking cessation is a realistic and achievable goal. It has been proven in several studies that counseling by the physician has shown to improve quitting rates. Other measures useful in helping the patient to quit smoking are assistance with pharmacologic adjuncts such as nicotine replacement therapy, varenicline or bupropion and referral to smoking cessation groups.

Follow-up of smoking status and repeated smoking cessation messages should be performed at each encounter. Smoking cessation messages can be reinforced through telephonic messages or even letters. The key to successful

smoking cessation is the understanding on the part of physician that inability to quit or relapse after quitting is due to strong physical addiction and does not imply the lack of will or moral weakness on the patient's part.

Hence smoking cessation efforts require perseverance of the patient as well as the physician in pursuing this ideal goal to halt the disease progression. Exposure to respiratory irritants should be avoided in COPD patients as this can accelerate the decline in lung function.

NICOTINE REPLACEMENT THERAPIES

A wide variety of nicotine replacement formulations have been developed. These include tablets, polacrilex (gum), transdermal systems, nasal spray, a variety of inhalers, and nicotine toothpicks. Five formulations are currently approved as aids for smoking cessation in the United States, and three are available over the counter. All have demonstrated about twofold increases in quit rates above placebo in clinical trials.

PHARMACOLOGIC THERAPY

BUPROPION

Bupropion, an antidepressant, has been demonstrated to be an effective aid in smoking cessation. In clinical trials, bupropion has doubled the quit rates

compared with placebo. It acts by potentiating dopaminergic and noradrenergic signaling.

Patients with a history of depression, but did not benefit from nicotine replacement appeared to benefit from bupropion. Bupropion may be a superior initial choice in such individuals. Combination of nicotine replacement with bupropion has been proven to be more effective than either agent alone.

The currently recommended dose is 150 mg daily for 3 days followed by 150 mg twice daily. The quit date should be after a week of therapy so that blood levels are established.

The drug is generally well tolerated. Side effects are dry mouth and insomnia. In combination with nicotine replacement an increase in blood pressure may also occur. A reduction in seizure threshold occurs. Hence the drug is contraindicated among those predisposed to seizures, or with anorexia nervosa or bulimia.

The appropriate duration of therapy is not established. Clinical trials that formed the basis for approval treated for 7 weeks. However, with prolonged

therapy, there is an increase in secondary quits, and therapy for 1 year, resulted in more quits than therapy for 7 weeks.

OFF-LABEL AGENTS

CLONIDINE

Clonidine is an α-adrenergic agonist, centrally acting antihypertensive. A number of clinical trials have evaluated its efficacy in smoking cessation and is proven to be effective.

NORTRIPTYLINE

Nortriptyline is a tricyclic antidepressant that has been evaluated for efficacy in smoking cessation in several studies. Both individual studies and a meta-analysis support its benefit as an aid to smoking cessation, and it is also recommended as a possible second-line agent.

A number of other agents approved for other uses have also been assessed for smoking cessation. None are currently recommended off-label by established guidelines.

These include

1. **Topiramate**, an antiepileptic that has shown promise for combined alcohol and tobacco addiction.

2. **Selegiline**, an agent used in the treatment of Parkinson's disease that has also shown promise in smoking cessation.
3. Several other agents, including selective serotonin reuptake inhibitors (SSRIs) antidepressants, opiate antagonists, anxiolytics and amphetamines have been demonstrated to be without benefit.

Several drugs are under active investigation for smoking cessation.

Varenicline is a nicotine receptor partial agonist that has looked promising in phase 2 and 3 clinical trials. As a partial agonist, it has the potential to mitigate some of the nicotine withdrawal syndrome. Also, as a partial agonist, it may function as an inhibitor and block some nicotine effects, and thus may prevent full relapse.

Rimonobant is a CB1 receptor antagonist. It appears to attenuate a wide variety of cravings and has shown promise in clinical trials for smoking and for obesity.

VACCINATION

Although the evidence of its particular efficacy in COPD is lacking *Pneumococcal vaccination* is recommended. Annual *influenza immunization* can prevent or attenuate this potentially fatal infection. The killed vaccine is

preferred, as cold attenuated live influenza vaccines have not been approved for use in older patients and those with underlying lung disease.

For individuals who are not immunized, prophylaxis with amantadine or rimantadine during an influenza epidemic can often prevent infection with influenza A. Due to the emergence of resistant strains and side effects these drugs have limited usefulness. During influenza epidemics, the use of neuraminidase inhibitors such as zanamivir and oseltamivir can minimize severity of infection if taken within 48 hours of onset of illness and are useful against both influenza A and B, and may limit the spread of infection.

ALPHA 1 ANTI TRYPSIN REPLACEMENT

*It is indicated in in*dividuals with severe deficiency. Studies have demonstrated that individuals with moderate degrees of impairment (FEV1 35 to 65 percent predicted) appear to benefit most in terms of preservation of lung function and improved survival. The human plasma-derived preparation of α1-antitrypsin is administered intravenously in a dose of 60 mg/kg weekly.

EXERCISE AND REHABILITATION

Regular prudent self-directed exercise is recommended for all individuals with COPD. This helps to prevent the muscle deconditioning that often accompanies the disorder. Individuals should be encouraged to perform at least

20 to 30 minutes of constant low-intensity aerobic exercise such as walking at least three times per week. Even the most severely impaired patients with COPD can usually attain an exercise regimen of 30 minutes of walking at 1 mph (i.e., one-half mile in 30 minutes). It is important to instruct patients that they should exercise to a level of dyspnea that is tolerable for the entire exercise period.

NUTRITION SUPPORT

About 50 % of patients with very severe COPD (FEV1 less than 35 percent of predicted value) show protein-calorie malnutrition. The possible mechanisms include increased resting metabolic demands, inadequate caloric intake due to dyspnea and anorexia, and production of cachexia-associated inflammatory cytokines such as TNF-α, IL-1, and IL-6.

Patients with a BMI of less than 90 percent of normal have increased mortality and decreased exercise capacity. Muscle wasting and loss of bone mass may be present even in patients who have normal BMI.

It is prudent to monitor body weight in COPD patients and encourage caloric supplementation as needed since those patients who do gain weight show improved survival. But clinical trials of nutritional supplementation have not been proven effective.

High-fat diets have the theoretical advantage of offering higher caloric content with lower CO2 production than high carbohydrate diets, but there is no convincing evidence that this strategy is clinically superior to a well-balanced diet. For patients with less advanced disease, a balanced diet with avoidance of overweight or underweight is a rational goal.

SLEEP DISORDERS IN COPD

Sleep disturbances are often overlooked in COPD. These are common symptoms in patients with COPD, including insomnia and daytime hypersomnolence. The causes for sleep symptoms are multifactorial and include anxiety/panic disorder due to fear of suffocation while sleeping, depression, resting hypoxemia, nocturnal bronchospasm, sleep apnea, associated diseases such as obstructive sleep apnoea and gastro esophageal reflux disease and nocturnal oxygen desaturation. In patients with COPD and sleep disturbances these causes should be sought and treated accordingly to improve the quality of life.

LONG TERM OXYGEN THERAPY

Apart from smoking intervention in early COPD, treatment of resting daytime hypoxemia with oxygen is a treatment that prolongs survival.

The two strongest indications for prescription of long-term oxygen therapy are:

1. Resting room-air $PaO_2 \leq 55$ mmHg or oxygen saturation ≤ 88 percent while a person is in usual state of health; and
2. Resting room-air PaO_2 56 to 60 mmHg or oxygen saturation 88 to 89 percent with supporting evidence of chronic hypoxemia such as polycythemia, pulmonary hypertension, cor pulmonale, or psychological impairment.

Oxygen is usually administered by nasal cannula, with the flow rate adjusted to maintain a resting saturation greater than 90 percent. The usual starting flow rate is 2 L/min, although some patients with severe hypercapnia require lower flows.

The most convenient and cost-effective oxygen source at home is usually a concentrator device that uses a molecular sieve to extract oxygen from room air. For ambulation, small compressed air cylinders or liquid oxygen reservoirs that can be carried provide patients with the ability to leave their homes. Ideally, oxygen should be used constantly 24 hours per day or at least 18 hours of

oxygen per day, however, substantial improvement has been demonstrated with use over 12 hours per day. If continuous oxygen supplementation is prescribed following an exacerbation of COPD, it is recommended to check arterial oxygen levels in 6months, as many patients will no longer require oxygen.

Smoking or exposure to any open flame, of course, is dangerous and prohibited in those who use oxygen.

Transtracheal oxygen administered via a percutaneous catheter is useful for patients who need high oxygen concentrations or in whom use of a nasal cannula is not tolerated because of local nasal adverse effects or cosmetic preference. Transtracheal oxygen has the advantage of decreasing effective dead space ventilation and permitting lower flow rates to provide high oxygen concentrations. Complications include local infection, pneumothorax and pneumomediastinum.

TREATMENT OF ANEMIA

Anemia present in about 10 percent of patients with severe COPD, similar to other chronic inflammatory diseases, and is a poor prognostic indicator. Patients with COPD have a lower erythropoietic response to hypoxia than healthy people at altitude. For patients who are anemic and breathless, restoration of normal hemoglobin content reduces resting minute ventilation and work of breathing, which presumably improves exercise capacity.

DRUG THERAPY

Bronchodilators and anti-inflammatory agents are used in COPD to reverse bronchoconstriction and improve airflow limitation. The goals of drug therapy are not only to improve lung function, but also to improve quality of life, exercise capacity, and prevent exacerbations. No drug treatment is known to diminish the decline in pulmonary function with continued smoking, or substantially reduce mortality.

Inhaled bronchodilators are the cornerstone in the symptomatic management of COPD. They are given on a regular basis to maintain bronchodilation and as and when needed to relieve symptoms. Both beta-agonist and anticholinergic classes are available in short duration (4- to 6-hour) and long-duration (12- to 24-hour) forms. The choice of bronchodilator class and duration of effect depends upon the preference of the patient and the cost.

Combination of different classes of bronchodilators is often more effective than increasing the dose of a single agent, and combination inhalers can simplify treatment regimens. Patients with advanced COPD often use a combination of bronchodilators, including long acting maintenance anticholinergics and beta agonists as well as symptomatic use of shorter-acting bronchodilators. Individuals with frequent exacerbations often benefit from a combination inhaler of corticosteroids and long-acting bronchodilator.

Long-acting oral preparations of theophylline are useful adjuncts in cases in which inhaled medication is too expensive or not acceptable for the patient.

Chronic use of systemic corticosteroids should be reserved for individuals with very frequent or life-threatening exacerbations who cannot tolerate their discontinuation. Response to treatment is judged by symptomatic improvement and functional status. Patients on long-term systemic steroids should receive prophylaxis for osteoporosis with calcium and vitamin D or bisphosphonates and should be instructed about the need for stress-dose steroids for acute illnesses.

Inhaled corticosteroids are most useful in patients who have an overlap with asthma and in advanced disease who have frequent exacerbations. Inhaled corticosteroids can reduce the frequency of exacerbations, improve airways reactivity, and quality of life. Inhaled corticosteroids, although poorly absorbed, probably do contribute to steroid side effects such as cataracts, capillary fragility, and osteoporosis in susceptible individuals. Hence it is prudent to prescribe the lowest effective dose. In patients who are at risk for osteoporosis (i.e., older age, cigarette smoking, and low exercise) as most patients with COPD are, it is prudent to recommend prophylactic treatment such as calcium supplements and vitamin D. In those with established osteoporosis, bisphosphonates are advised.

COMPLICATIONS OF COPD

1. Acute exacerbation of COPD
2. Pneumothorax.
3. Hypercapnia.
4. Cor pulmonale.
5. Supraventricular arrhythmias.
6. Respiratory failure.

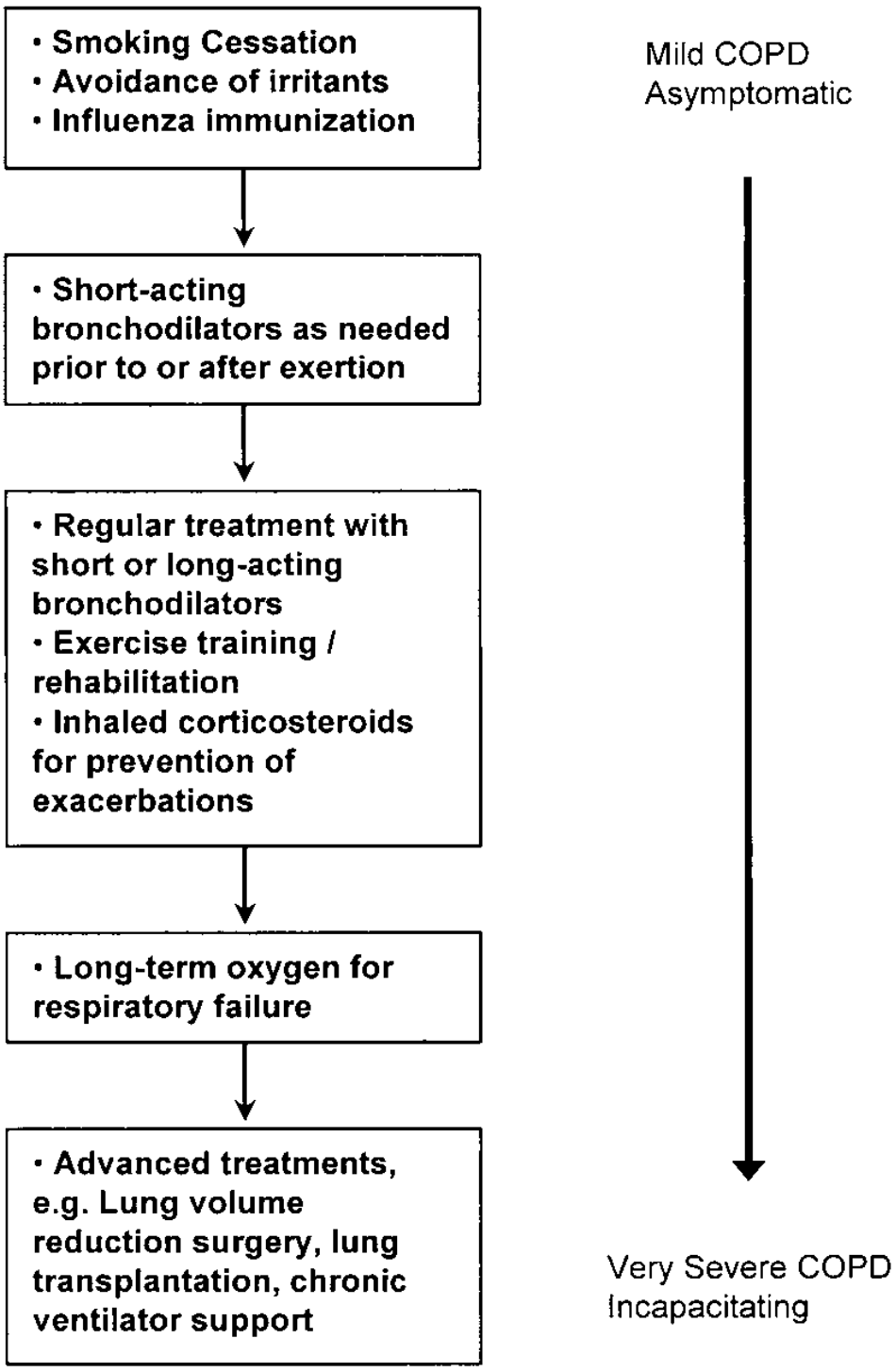


FIGURE 2: STEPWISE ALGORITHM FOR MANAGEMENT OF COPD

Indications for Hospital Assessment or Admission for COPD Exacerbation[10]

- Sudden onset of new or severe symptoms (e.g., dyspnea).

Figure 1STEPWISE ALGORITHM FOR THE MANAGEMENT OF COPD

- Inability to sleep or eat because of dyspnea.
- Severe or very severe underlying COPD.
- Onset of new physical findings (e.g., edema, cyanosis, change in mental status).
- Failure to respond to initial medical treatment.
- Associated comorbidities (e.g., cardiac, renal, hepatic failure, or diabetes).
- Diagnostic uncertainty (e.g., suspected pneumonia or pulmonary embolism).
- Unusual presenting symptoms.
- Older age or frailty.
- Inadequate home or social support.
- History of poor adherence with treatment.

Indications for ICU Admission for COPD Exacerbation

- Severe dyspnea unresponsive to initial treatment.
- Change in mental status (e.g., confusion, lethargy, coma).
- Persistent or worsening hypoxemia, hypercapnia, or respiratory acidosis.
- Need for sedation or narcotic pain control.

GLOMERULAR FILTRATION AS A MARKER OF RENAL FUNCTION:

Glomerular filtration rate (GFR) is considered to be the optimal test for the assessment of renal function. It is the volume of fluid filtered from the renal glomerular capillaries into the Bowman's space per unit time. It is the product of average filtration rate of nephron multiplied by the total number of nephrons in both kidneys[11].

The normal GFR varies according to age, sex, body size, physical activity, diet, pregnancy, drug intake etc.[12].The normal GFR is 130 ml/min/1.73 sq. m body surface area in males. The normal GFR in females is 120 ml/min/1.73 sq. m. GFR is 8% higher in young men than women. GFR also falls by 10% during midnight. GFR increases by 50% during the first trimester of pregnancy but becomes normal after delivery. GFR decreases with increasing age. It falls by approximately 0.75 ml/min /year after 40 years of age. An important pitfall in using the GFR for estimating renal function is that GFR might remain normal despite substantial reduction in renal function.

GFR cannot be measured directly. It is measured as the urinary clearance of a chemical either endogenous or exogenous. The ideal chemical should have

a steady level in the plasma, should be freely filtered but neither reabsorbed nor secreted by the renal tubules.

GFR is calculated as follows

GFR = (urine concentration x urine flow)/plasma concentration.

Creatinine is the most commonly used endogenous filtration marker in the estimation of GFR by calculating creatinine clearance. Creatinine is produced by the breakdown of creatine phosphate in muscle. Other sources are intake of meat in diet or creatine supplements. It is freely filtered by the glomeruli but actively secreted by tubules. Drugs inhibiting tubular secretion of creatinine can increase the serum creatinine levels. Patients with decreased muscle mass can have low serum creatinine levels.

Creatinine clearance (C Cr) is calculated from the concentration of creatinine in a collected sample of urine (U Cr), urine flow rate (V), and plasma creatinine concentration (P Cr).

C Cr = (U Cr x V)/P Cr.

Creatinine clearance is not measured routinely to estimate GFR due to difficulty in measuring creatinine concentration in 24 hour urine sample.

As an alternative to the cumbersome procedure of measuring creatinine clearance directly several methods of estimating creatinine clearance were devised such as

1. Cockroft – Gault formula.
2. MDRD (modification of diet in renal disease) formula.
3. CKD EPI (chronic kidney disease epidemiology collaboration) formula.

HYPONATREMIA

The normal serum sodium ranges from 135 -145 mEq/L. Hyponatremia is defined is serum sodium < 135 mEq/L. Sodium is the principal extracellular cation which determines the extracellular fluid osmolarity. Sodium plays an important role in regulating the osmolarity of extracellular fluid and effective

circulating blood volume. The movement of sodium across cell membrane is an energy dependent process and requires Na-K ATPase pump.

Normal diet provides 4-7 g of sodium per day. One teaspoon of table salt has 6 g NaCl of which sodium constitutes 2.4 g. 1 g of sodium is equivalent to 43 mEq of sodium. 1 g of NaCl yields 17 mEq of sodium.

In the kidneys 60% of filtered sodium is reabsorbed in the proximal tubule by Na^+ H^+ exchange. In the thick ascending limb of Henle's loop 30% of filtered sodium is reabsorbed via the Na^+ K^+ $2Cl^-$ cotransporter. 7% is reabsorbed in the distal convoluted tubule through the Na^+ Cl^- cotransporter. The remaining 3% of filtered sodium reaches the collecting duct. Sodium absorption in this portion of nephron takes place through epithelial sodium channels regulated by aldosterone. Sodium is actively reabsorbed in all the segments of nephron except the thin portions of the loop of Henle.

The kidneys reabsorb 96 – 99% of the filtered sodium. The urine sodium excretion varies from <1 mEq to >400 mEq/ day depending on the sodium content in diet. The changes in the renal excretion of sodium is brought by changes in GFR and changes in the tubular sodium reabsorption especially in the 3% of the filtered sodium that reaches the collecting ducts[13].

The factors regulating sodium reabsorption are

1. The circulating aldosterone levels.

2. Other adrenocortical hormones.
3. Circulating ANP levels.
4. Rate of tubular secretion of potassium and hydrogen ions.

Hyponatremia can be classified into different types [11].

1. Translocational hyponatremia.
2. Pseudohyponatremia.
3. Hypovolemic hyponatremia.
4. Euvolemic hyponatremia.
5. Hypervolemic hyponatremia.

TRANSLOCATIONAL HYPONATREMIA

Osmotically active substances in the extracellular fluid can draw water from inside the cell into the extracellular compartment leading to an apparent hyponatremia. For example in hyperglycemic states such as diabetic ketoacidosis every 100 mg/dl rise in plasma glucose level above the normal

value of 100 mg/dl can decrease the plasma sodium by 1.6 m mol/L. Other osmotically active substances such as mannitol, glycine can also lead to this type of hyponatremia.

PSEUDOHYPONATREMIA

In hypertryglyceridemias and paraproteinemias the solid phase of plasma is greatly increased. This can lead to apparently low serum sodium levels. This is prevented by measuring serum sodium by direct and indirect ion sensitive potentiometry.

HYPOVOLEMIC HYPONATREMIA

This can be caused by renal or extrarenal fluid loss such as excessive diuretics, mineralocorticoid deficiency, salt losing nephropathy, diarrhoea, vomiting etc. The hypovolemia causes stimulation of thirst and non-osmotic release of ADH. Water retention occurs and resuts in hyponatremia.

EUVOLEMIC HYPONATREMIA

In this condition the total body water is increased but there is no change in the total body sodium. Causes include hypothyroidism, glucocorticoid deficiency, and drugs like clofibrate, haloperidol, amitryptiline, NSAIDS, sertraline and SIADH.

HYPERVOLEMIC HYPONATREMIA

In this condition both the total body water and sodium are increased, the increase in total body water is more than the increase in total body sodium. It is caused by nephrotic syndrome, cirrhosis and congestive cardiac failure.in these disease states the underfilling of the arterial circulation causes stimulation of the renin angiotensin aldosterone system leading to the retention of salt and water. Stimulation of the ADH release causes water retention. The severity of hyponatremia in these conditions is a prognostic marker of the underlying disease.

CLINICAL FEATURES OF HYPONATREMIA

At serum sodium levels >125 the patients are usually asymptomatic. At levels less than 125 patients can have symptoms such as headache, lethargy, nausea, seizures and coma, respiratory depression and death due to increase in intracranial pressure.

The increase in intracranial pressure is due to osmotic shift of water into the neurons as a result of hypo osmolarity of the extracellular fluid. Elderly patients are usually asymptomatic even at serum sodium levels<120 mEq/L. This is due to cerebral atrophy and the increased space available within the cranium for the brain to expand. Children are particularly susceptible to the effects of hyponatremia due to the high ratio of brain to skull volume.

CENTRAL PONTINE MYELINOLYSIS

Rapid correction of hyponatremia is suicidal and can result in osmotic demyelination syndrome. This rapid correction of serum sodium levels can cause movement of water from within the cells to the ECF. This rapid shrinkage when it occurs in the neurons can lead on to osmotic demyelination syndrome or central pontine myelinolysis.

The more severe form of the disease is characterized by flaccid paralysis, dysarthria and dysphagia. Diagnosis can be confirmed by CT or MRI brain.

Risk of this catastrophic complication is increased in chronic hyponatremia >48 hrs duration, pre-existing hypokalemia, malnutrition, alcoholism and children.

To prevent this complication, correction of hyponatremia should be gradual and guided by frequent monitoring of the patients clinical condition and serum sodium levels. If the patient is acutely symptomatic such as in coma or seizures hyponatremia can be corrected at the rate of 1-2 mEq/L for 3-4 hrs. Once the patient's clinical condition improves the rate of correction should be more gradual such that rate of increase in serum sodium should not exceed 10-12 mEq/L in a 24 hr period. In chronic hyponatremia the correction should not exceed 6-8 mEq/L in a 24 hr period.

RENAL FAILURE AND HYPONATREMIA IN COPD

Edema and hyponatremia are found in a large proportion of patients with COPD. The cause of edema in COPD was thought to be cor pulmonale ie the hypoxia induced by COPD causes pulmonary hypertension, right ventricular

hypertrophy and eventually right heart failure. Later it was found that edema in COPD could not be attributed to cor pulmonale as cardiac output was found to be adequate for the body's metabolic demands in most such patients unless they had significant underlying cardiac disease[14,15].

In 1960, **Campbell and Short** observed that edema in COPD patients is invariably associated with carbon-di-oxide retention[16]. This observation has lead to a change in our understanding of the pathogenesis of edema in COPD. Hypercapnia causes local adrenergic discharge which results in renal vasoconstriction and reduced renal plasma flow but the glomerular filtration rate is preserved until the late stages of the disease. The normal glomerular filtration despite the reduced renal plasma flow increases the filtration fraction and peritubular oncotic pressure. This leads to sodium and water retention[17]

Other mechanisms such as enhanced renal tubular sodium reabsorption through Na^+-H^+ exchange in response to hypercapnia and respiratory acidosis and imbalance in hormones that regulate sodium and water imbalance are also implicated[18]. PaCO2 has been found to inversely correlate with renal plasma flow and sodium and water excretion.

	Mild to severe	*Very severe*
Blood gases		
P_{aCO_2}	Hypercapnia	Hypercapnia
P_{aO_2}	Mild hypoxaemia	Severe hypoxaemia
Renal function		
ERPF	Reduced	Severely reduced
FF	Increased	Markedly increased
GFR	Normal	Reduced
Water excretion	Impaired	Markedly impaired
Na^+ excretion	Impaired	Impaired
Hormones		
Catecholamines	Increased	Markedly increased
PRA	Normal or increased	Increased
PA	Normal or increased	Increased
AVP	Normal	Increased
ANP	Normal	Increased
Na^+ and water homeostasis		
Oedema	Rare	Frequent
Hyponatraemia	Absent	Possible

P_{aO_2}, P_{aCO_2} = arterial oxygen and carbon dioxide tensions; ERPF = effective renal plasma flow; FF = filtration fraction; GFR = glomerular filtration rate; PRA = plasma renin activity; PA = plasma aldosterone; AVP = arginine vasopressin; ANP = atrial natriuretic peptide.

TABLE 4: CHANGES IN THE RENAL HEMODYNAMICS AND HORMONES REGULATING SODIUM AND WATER BALANCE IN PATIENTS WITH MILD TO MODERATE COPD AND SEVERE COPD

Table 4 depicts the changes in renal plasma flow, glomerular filtration and changes in various hormones that regulate sodium and water balance in patients with mild to moderate and severe COPD .These changes are triggered by carbon dioxide retention.

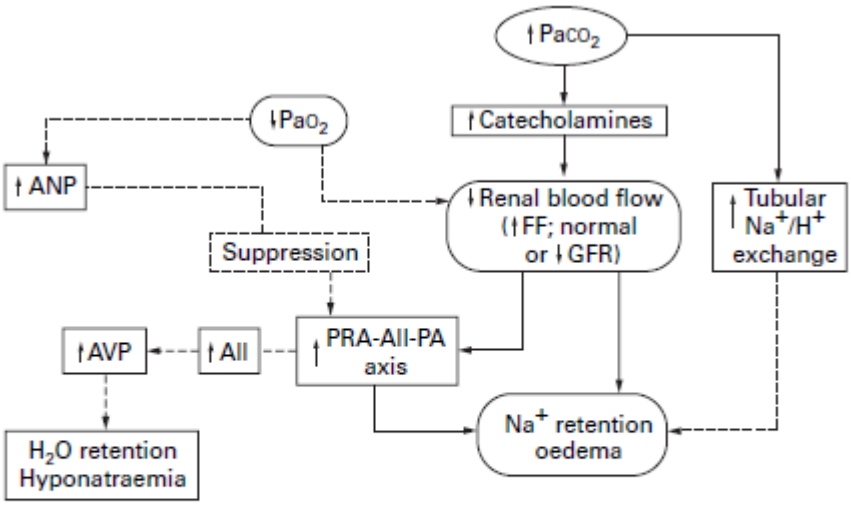


Figure 1 Renal and hormonal abnormalities induced by chronic hypercapnia and possibly aggravated by severe hypoxaemia in the pathogenesis of sodium and water retention in COPD. Solid lines indicate established mechanisms; broken lines indicate non-proven pathways. ANP = atrial natriuretic peptide; AVP = arginine vasopressin; GFR = glomerular filtration rate; PRA = plasma renin activity; AII = angiotensin II; PA = plasma aldosterone; FF = filtration fraction; Pa_{O_2}, Pa_{CO_2} = arterial oxygen and carbon dioxide tensions. Modified from Farber and Manfredi.[6]

FIGURE 3: PATHOGENESIS OF EDEMA AND HYPONATREMIA IN COPD PATIENTS

HORMONAL ABNORMALITIES IN COPD

During the early stages of COPD the carbon-di-oxide retention causes an increase in the renal sympathetic tone and sodium retention[19, 20, 21]. Early in the disease course the carbon-di-oxide retention causes decrease in the renal plasma flow without compromising the GFR. As the disease progresses when the GFR

starts to fall the renin angiotensin aldosterone system is activated which results in sodium and water retention [22, 23, 24].

Another proposed mechanism for sodium and water retention leading to edema is as follows. Hypercapnia in COPD induces dilatation of the precapillary sphincters causing under filling of the arterial system. This stimulates the renin angiotensin aldosterone system. The resulting sodium and water retention is unable to fill the dilated arterial system creating a vicious cycle of sodium retention and massive edema.

In a number of edematous patients with COPD significant hyponatremia is present. Plasma antidiuretic hormone (ADH) levels are inappropriately elevated in these patients that is inappropriate for the level of plasma osmolarity [25,26]. In normal individuals ADH release is primarily controlled by plasma osmolarity. An increase in the plasma osmolarity stimulates ADH release resulting in water retention and restoration of plasma osmolarity to normalcy. The proposed mechanisms for the elevated ADH are stimulation of ADH

release by angiotensin II, stimulation of baroreceptors in edematous patients with low circulating blood volume[28, 29].

As in patients with congestive heart failure COPD patients also have elevated levels of atrial natriuretic peptide (ANP) [27]. In normal subjects elevated ANP causes prompt natriuresis and suppression of plasma renin angiotensin system (PRA). It is not clear why the elevated ANP is not able to cause natriuresis in COPD patients. It is proposed that the stimulatory effect of reduced renal plasma flow on PRA system probably overwhelms the inhibitory effect of elevated ANP levels on the PRA system [30, 31, 32, 33].

The onset of edema is proven to be a poor prognostic marker. These patients have a 4 year mortality of 73% as compared to 53% for the whole group [13].With the understanding of the mechanisms underlying sodium and water retention in COPD it is clear that the therapeutic intervention required to control the edema in COPD is quite different from that used in congestive heart failure. The optimal therapeutic strategy should be the reversal of hypoxemia and improvement of the lung mechanics by reducing bronchial secretion and promoting maximal bronchodilation.

The role of non-invasive mechanical ventilation in reducing hypercarbia has not been investigated. Hyponatremia should be treated with water restriction. The use of ACE inhibitors is a subject of debate. Digitalis should be avoided unless the patient has an intrinsic cardiac disease with a documented low cardiac output since this drug can increase the risk of arrhythmias in the presence of hypoxemia. Diuretics should probably be used with caution since it can cause hypochloremic metabolic alkalosis which can precipitate respiratory depression, worsening of the blood gas tension and further worsening of the edema by the mechanisms discussed above.

ASSOCIATION OF CHRONIC RENAL FAILURE WITH COPD

Chronic renal failure (CRF) increases in prevalence with age[34]. In elderly who constitute the majority of the population affected by chronic diseases the muscle mass is frequently decreased. In these elderly patients serum creatinine which is routinely used in clinical practice as a marker of renal function can be within normal limits despite severe reduction in the renal function assessed by the glomerular filtration rate. This is called as concealed or unrecognized CRF[39].

Chronic renal failure is associated with several chronic diseases such as congestive heart failure and diabetes [35, 36]. The association of chronic renal

failure with chronic diseases has therapeutic implications and it frequently implies a poor prognosis [37, 38]. The association of COPD with CRF has been investigated in a few studies which show that COPD is significantly associated with CRF. COPD is commonly associated with coronary artery disease (CAD) which can be associated with renal vascular disease [40, 41]. Nicotine and selected heavy metals found in cigarette smoke are known to cause renal disease [42]

MATERIALS AND METHODS

AIMS AND OBJECTIVES

1. To compare the incidence of renal failure and hyponatremia among patients admitted with Chronic Obstructive Pulmonary Disease (COPD) and age matched control population.
2. To determine whether the incidence of renal failure and hyponatremia is more among COPD patients when compared with age matched control population.

PLACE OF STUDY:

Department of General Medicine, Government Stanley Medical College and Hospital.

DURATION OF STUDY:

May 2012 – October 2012.

INCLUSION CRITERIA:

Patients who are previously diagnosed to have COPD based on clinical features and spirometry in the department of thoracic medicine who get admitted in medicine wards will be included in the study.

EXCLUSION CRITERIA:

Patients with COPD who have other comorbid illness which are likely to cause renal failure are excluded.

These comorbid illness include

- Diabetes.
- Hypertension.
- Known renal disease such as renal stones, polycystic kidney disease etc.
- Coronary artery disease.
- Cardiac failure.
- Cirrhosis.
- Ingestion of nephrotoxic drugs.

SELECTION OF CONTROL POPULATION

Control population included age and sex matched persons without COPD and other illness known to affect renal function which are listed above.For each COPD patient one control patient was selected.

METHODOLOGY:

COPD patients who fulfilled the study criteria were included. A total of 56 patients were included. They were subjected to detailed history taking, clinical examination and investigations which included

- Chest x ray P A view.
- Sputum examination.
- Blood urea.
- Serum creatinine.
- Serum electrolytes.
- Complete blood count.
- Liver function tests.
- Urine analysis.

For each COPD patient one age and sex matched control was selected.the control group of patients were also subjected to similar investigations.

The creatinine clearance was estimated using the four variable MDRD formula. A creatinine clearance of <60 is defined as renal failure. This cutoff was based on the National Kidney Foundation's Kidney Diseases Outcome Quality Initiative Guidelines[43] which marks the threshold for moderate renal dysfunction.

- Serum sodium < 135 mEq/L is defined as hyponatremia.
- Serum albumin < 3.5 g/dL is defined as hypoalbuminemia.
- Hemoglobin < 13 g/ dL is defined as anemia in males.
- Hemoglobin <12 g/dL is defined as anemia in females.

The results were tabulated and analysed.

The incidence of renal failure, hyponatremia, anemia and hypoalbuminemia were compared among the COPD patients and the control group and analysed using SPSS2 software for statistical significance to determine whether these abnormalities are more prevalent among COPD patients when compared with control population.

RESULTS AND DISCUSSION

		Group				Total	
		Case		Control			
		N	%	N	%	N	%
SEX	Male	46	82.1	46	82.1	92	82.1
	Female	10	17.9	10	17.9	20	17.9
Total		56	100.0	56	100.0	112	100.0

TABLE 5: SEX DISTRIBUTION OF PATIENTS IN THE CASES AND CONTROL GROUPS

Total number of COPD patients included in the study: 56.

Number of males: 46.

Number of females: 10.

Total no. of control population: 56.

No. of males: 46.

No. of females: 10.

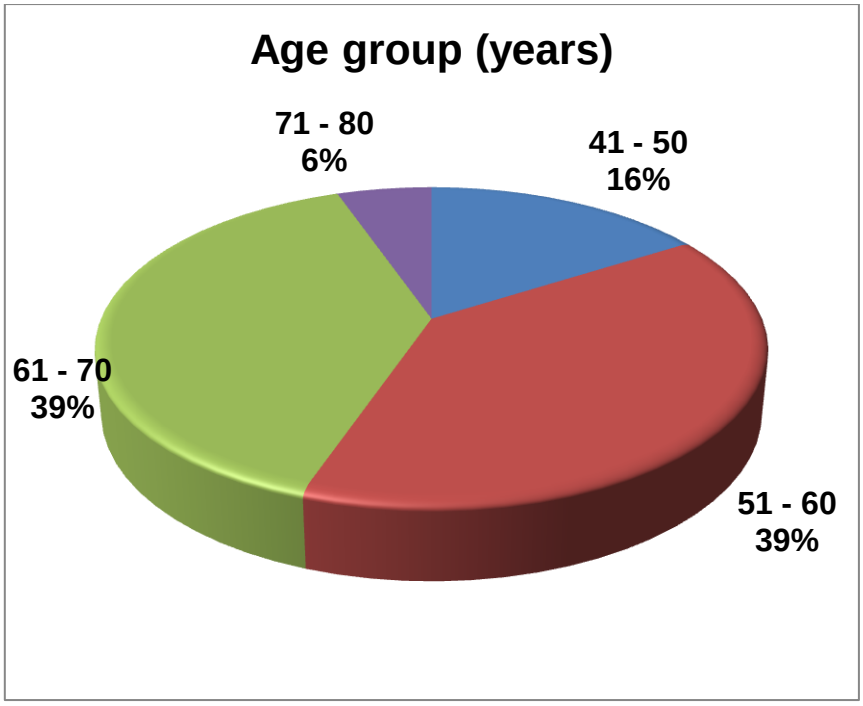
The sex distribution among the cases and controls were similar to ensure comparability.

	Group				Total	
	Case		Control			
	N	%	N	%	N	%

Age group (years)	**41 – 50**	9	16.1	9	16.1	18	16.1
	51 – 60	22	39.3	22	39.3	44	39.3
	61 – 70	22	39.3	22	39.3	44	39.3
	71 – 80	3	5.4	3	5.4	6	5.4
Total		56	100.0	56	100.0	112	100.0

TABLE 6: AGE DISTRIBUTION AMONG THE CASES AND CONTROLS

The age distribution among the cases and controls were similar. The majority of the patients were in the 51 - 70 year age group contributing to nearly 80% of the study population.



GRAPH 1: AGE DISTRIBUTION AMONG CASES AND CONTROL

Variables	Group	N	Mean	Std. Dev	P-Value
Hb	Case	56	12.07	3.06	0.058
	Control	56	13.01	2.00	

TABLE 7: COMPARISON OF HEMGLOBIN VALUES IN CASES AND CONTROLS

The mean Hb among cases was 12.07 g/dL vs 13.01g/dL among the control.

This difference was not statistically significant with a p value of 0.058.

Variables	Group	N	Mean	Std. Dev	P-Value
ALBUMIN	Case	56	4.00	0.56	0.375
	Control	56	4.09	0.57	

TABLE 8: COMPARISON OF ALBUMIN VALUES IN CASES AND CONTROLS

The mean albumin level among cases was 4 g/dL vs 4.09 g/dL among the control population. This difference was not statistically significant with a p value of 0.375.

Variables	Group	N	Mean	Std. Dev	P-Value
CREATININE	Case	56	1.15	0.43	0.001
	Control	56	0.91	0.34	

TABLE 9: COMPARISON OF CREATININE VALUES IN CASES AND CONTROLS

The mean creatinine among the cases was 1.15 mg/dL vs 0.91 mg/dL among the control group. This difference was statistically significant with a p value of 0.001.

Variables	Group	N	Mean	Std. Dev	P-Value

CREATININE CLEARANCE	Case	56	76.56	30.15	<0.001
	Control	56	98.36	33.61	

TABLE 10: COMPARISON OF CREATININE CLEARANCE VALUES IN CASES AND CONTROLS

The creatinine clearance was 76.56 ml/min/1.73 sq m among the cases.it was 98.36 ml/min/1.73 sq m among the control group. This difference was statistically significant with a p value of < 0.001.

Variables	Group	N	Mean	Std. Dev	P-Value
SODIUM	Case	56	131.78	7.37	<0.001
	Control	56	139.20	3.71	

TABLE 11: COMPARISON OF SODIUM VALUES IN CASES AND CONTROLS

The mean serum sodium among the cases was 131.78 m Eq/L vs 139.20 mEq/L among the control group. This difference was statistically significant with a p value of <0.001.

Variables	Group	N	Mean	Std. Dev	P-Value
POTASSIUM	Case	56	3.80	0.58	0.001
	Control	56	4.16	0.57	

TABLE 12: COMPARISON OF POTASSIUM VALUES IN CASES AND CONTROLS

The mean serum potassium among the cases was 3.80 mEq/L vs 4.16 mEq/L among the control. This difference was statistically significant with a p value of 0.001.

RENAL FAILURE AMONG CASES AND CONTROLS:

		Group				Total		P-Value
		Case		Control				
		N	%	N	%	N	%	
Creatinine	**< 60**	24	42.6	9	16.1	33	28.8	0.003

Clearance	**≥ 60**	32	57.4	47	83.9	79	71.2	
Total		56	100.0	56	100.0	112	100.0	

TABLE 13: RENAL FAILURE AMONG CASES AND CONTROLS

Creatinine clearance < 60 was defined as the cut off value for renal failure. Among the cases 24 of 56 i.e., 42.6% had creatinine clearance <60. Among the control group only 9 of the 56 i.e., 16.1% had creatinine clearance < 60.

Thus renal failure was more prevalent among the COPD patients than controls. This association was statistically significant with a p value of 0.003.

HYPONATREMIA AMONG CASES AND CONTROL

		Group				**Total**		**P-Value**
		Case		**Control**				
		N	**%**	**N**	**%**	**N**	**%**	
Sodium (Hyponatremia)	**< 135**	35	62.5	7	9.3	42	36.4	0.001
	≥ 135	21	37.5	49	90.7	70	63.6	
Total		56	100.0	56	100.0	112	100.0	

TABLE 14: HYPONATREMIA AMONG CASES AND CONTROLS

Serum sodium <135 m Eq/L is defined as hyponatremia. Among cases 35 out of 56 i.e. 62.5% had hyponatremia. Among controls, 7 of 56 i.e. 9.3% had hyponatremia.

Hyponatremia was more prevalent among COPD patients than the control group. This difference was statistically significant with a p value of 0.001.

HYPOALBUMINEMIA AMONG CASES AND CONTROLS:

		Group				Total		P-Value
		Case		Control				
		N	%	N	%	N	%	
Albumin level	< 3.5	12	21.4	6	10.7	18	16.1	0.123
	≥ 3.5	44	78.6	50	89.3	94	83.9	
Total		56	100.0	56	100.0	112	100.0	

TABLE 15: HYPOALBUMINEMIA AMONG CASES AND CONTROLS

Serum albumin < 3.5 g/dL is defined as hypoalbuminemia. Hypoalbuminemia was compared in the study as this might reflect malnutrition and muscle wasting which can contribute to low serum creatinine despite

significant decline in renal function. Hypoalbuminemia was present in 12 out of 56 i.e. 21.4% among cases. It was present in 6 of 56 patients i.e. 10.7% in the control group.

Though hypoalbuminemia was more prevalent among the COPD patients than the control population the difference was not statistically significant i.e. p value of 0.123.

PREVALENCE OF ANEMIA AMONG THE CASES AND CONTROL

		Group				Total		P-Value
		Case		Control				
		N	%	N	%	N	%	
Hb level	Low	21	37.5	13	23.2	34	30.4	0.100
	High	35	62.5	43	76.8	78	69.6	
Total		56	100.0	56	100.0	112	100.0	

TABLE 16: PREVALENCE OF ANEMIA AMONG THE CASES AND CONTROL

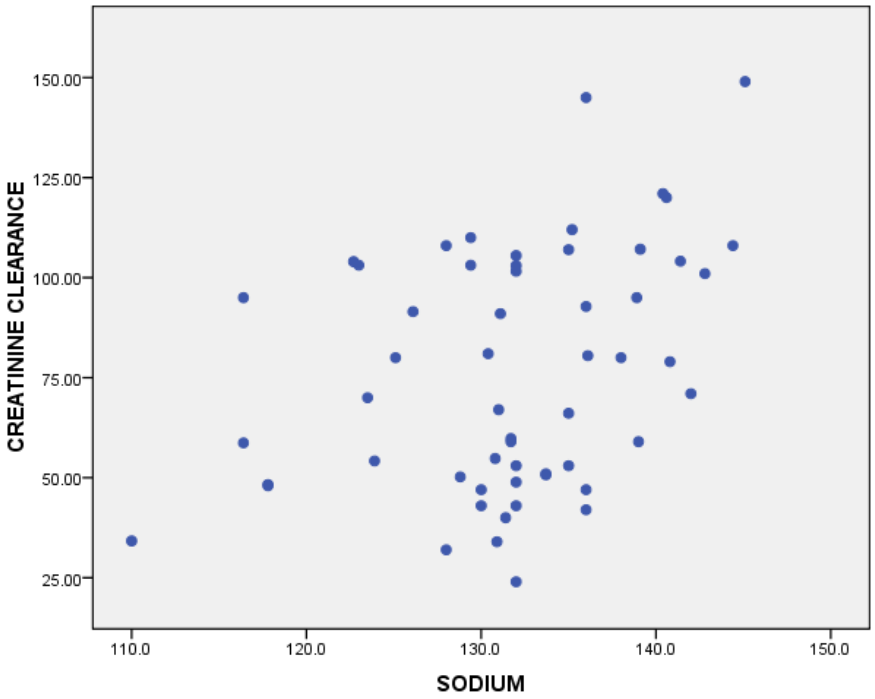
Hb < 13 g/dL is defined as anemia in males. Hb < 12 g/dL is defined as anemia in females. Anemia was compared among the cases and controls as it might correlate with declining renal function. Anemia was present in 21 of 56 patients ie 37.5% among cases. Anemia was present in 13 of 56 patients ie

23.2% among control group. Though anemia was more prevalent among the cases when compared with the control population the difference was not statistically significant with a p value of 0.100.

CORRELATION OF RENAL FAILURE WITH HYPONATREMIA

		SODIUM
CREATININE CLEARANCE	**Correlation**	0.367
	P-Value	0.005
	N	56

TABLE 17: CORRELATION OF RENAL FAILURE WITH HYPONATREMIA



GRAPH 2: SCATTER DIAGRAM DEPICTING THE CORRELATION BETWEEN SERUM SODIUM AND CREATININE CLEARANCE

Renal failure and hyponatremia were more prevalent among COPD patients than controls with a statistically significant difference.

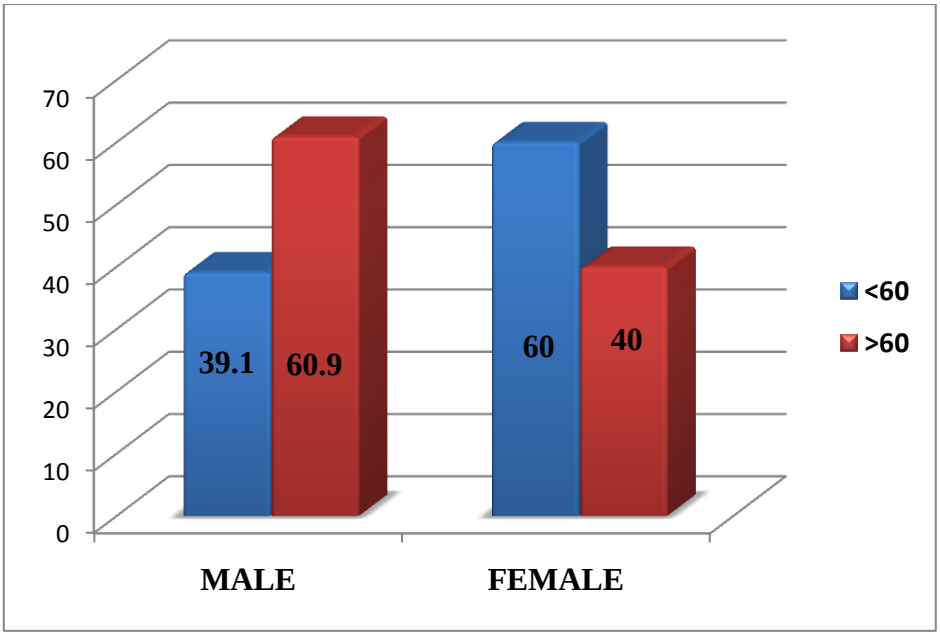
In order to find whether there was a correlation between declining renal function and the degree of hyponatremia a scatter diagram was plotted with serum sodium along X axis and creatinine clearance along Y axis.As the creatinine clearance decreased there was a decline in serum sodium levels. In other words with worsening renal failure degree of hyponatremia also worsened.

This positive correlation of creatinine clearance and serum sodium was statistically significant with a p value of 0.005.

RENAL FAILURE AMONG COPD PATIENTS:

		Creatinine Clearance				Total		P-Value
		< 60		≥ 60				
		N	%	N	%	N	%	
SEX	Male	18	39.1	28	60.9	46	100.0	0.198
	Female	6	60.0	4	40.0	10	100.0	
Total		24	42.6	32	57.4	56	100.0	

TABLE 18: RENAL FAILURE AMONG COPD PATIENTS



GRAPH 3: RENAL FAILURE AMONG COPD PATIENTS – SEX DISTRIBUTION

- Total no. of COPD patients - 56.
- No. of males - 46.
- No. of females - 10.
- No. of patients with renal failure - 24.
- No. of males with renal failure - 18.
- No. of females with renal failure - 6.
- 18 of 46 male COPD patients i.e. 39.1% had renal failure.
- 6 of 10 female COPD patients i.e. 60% had renal failure.

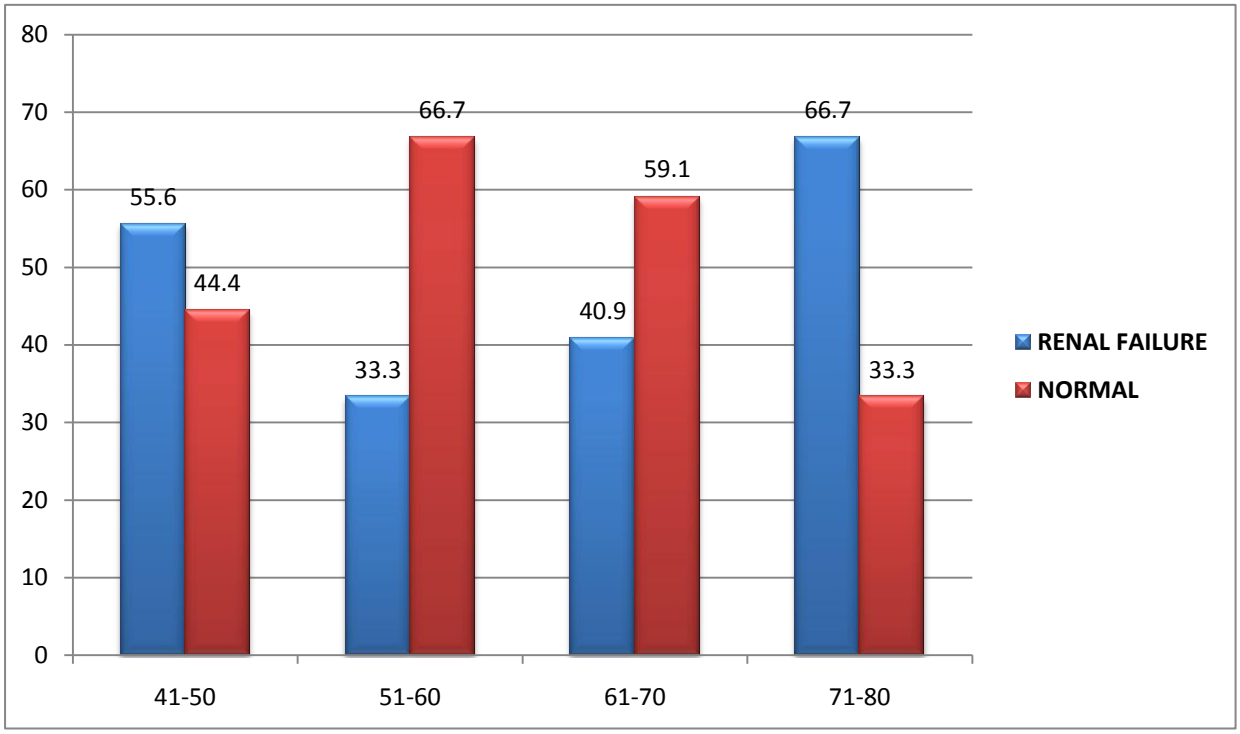
The reasons for the high prevalence of renal failure among females as compared with males are not known. This could probably be related to more severe disease which was present in these patients.

RENAL FAILURE AMONG COPD PATIENTS - AGE WISE DISTRIBUTION:

		Creatinine Clearance				Total		P-Value
		< 60		≥ 60				
		N	%	N	%	N	%	
Age group (years)	41 - 50	5	55.6	4	44.4	9	100.0	0.558
	51 - 60	8	33.3	14	66.7	22	100.0	
	61 - 70	9	40.9	13	59.1	22	100.0	
	71 - 80	2	66.7	1	33.3	3	100.0	
Total		24	42.6	32	57.4	56	100.0	

TABLE 19: RENAL FAILURE AMONG COPD PATIENTS - AGE WISE DISTRIBUTION

RENAL FAILURE AMONG COPD PATIENTS - AGEWISE DISTRIBUTION

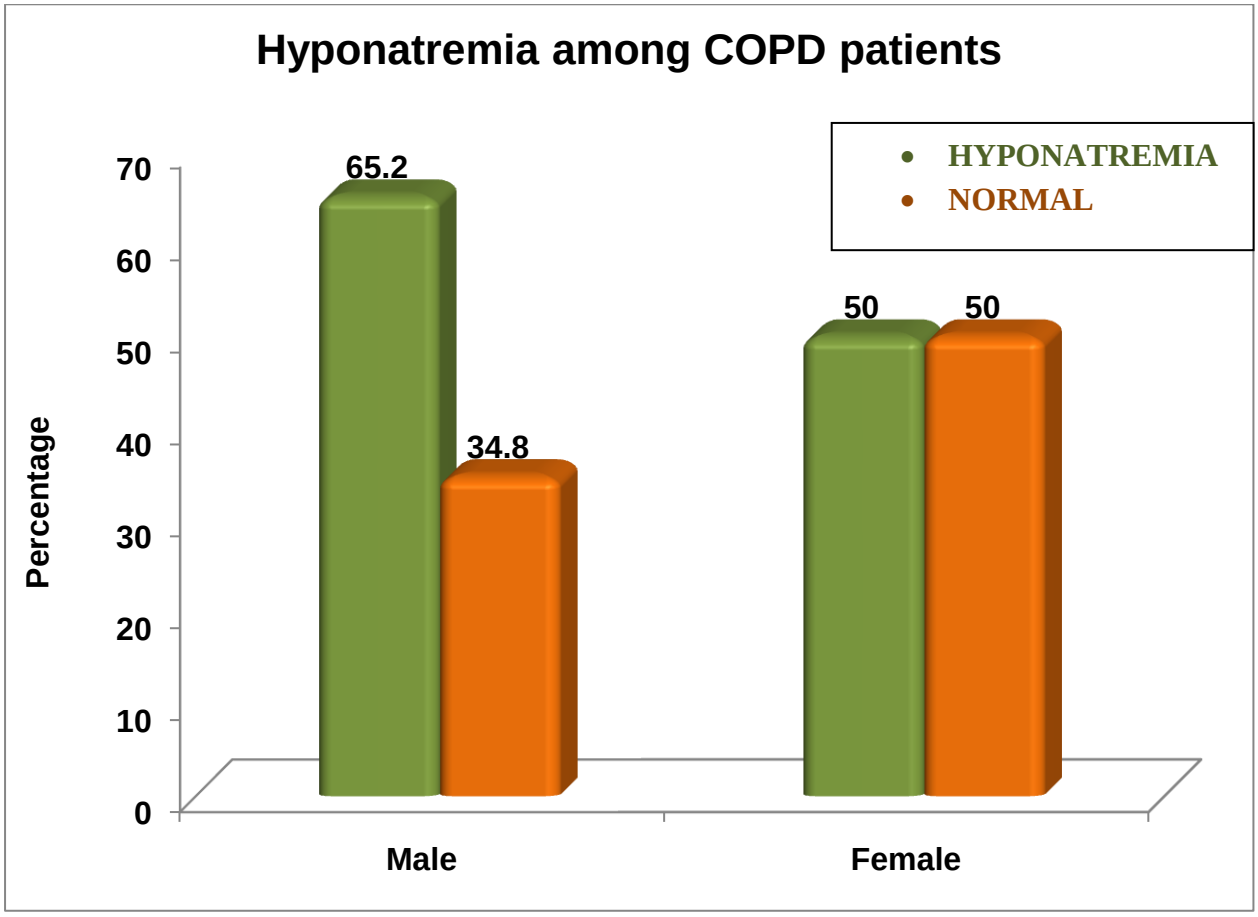


GRAPH 4: RENAL FAILURE AMONG COPD PATIENTS – AGEWISE DISTRIBUTION

HYPONATREMIA AMONG COPD PATIENTS – SEX DISTRIBUTION:

		Sodium (Hyponatremia)				Total		P-Value
		< 135		≥ 135				
		N	%	N	%	N	%	
SEX	Male	30	65.2	16	34.8	46	100.0	0.476
	Female	5	50.0	5	50.0	10	100.0	
Total		35	62.5	21	37.5	56	100.0	

TABLE 20: HYPONATREMIA AMONG COPD PATIENTS – SEX DISTRIBUTION



GRAPH 5: HYPONATREMIA AMONG COPD PATIENTS

Total no of COPD patients - 56.

No. of patients with hyponatremia - 35.

Total no of male COPD patients - 46.

No. of male COPD patients with hyponatremia - 30.

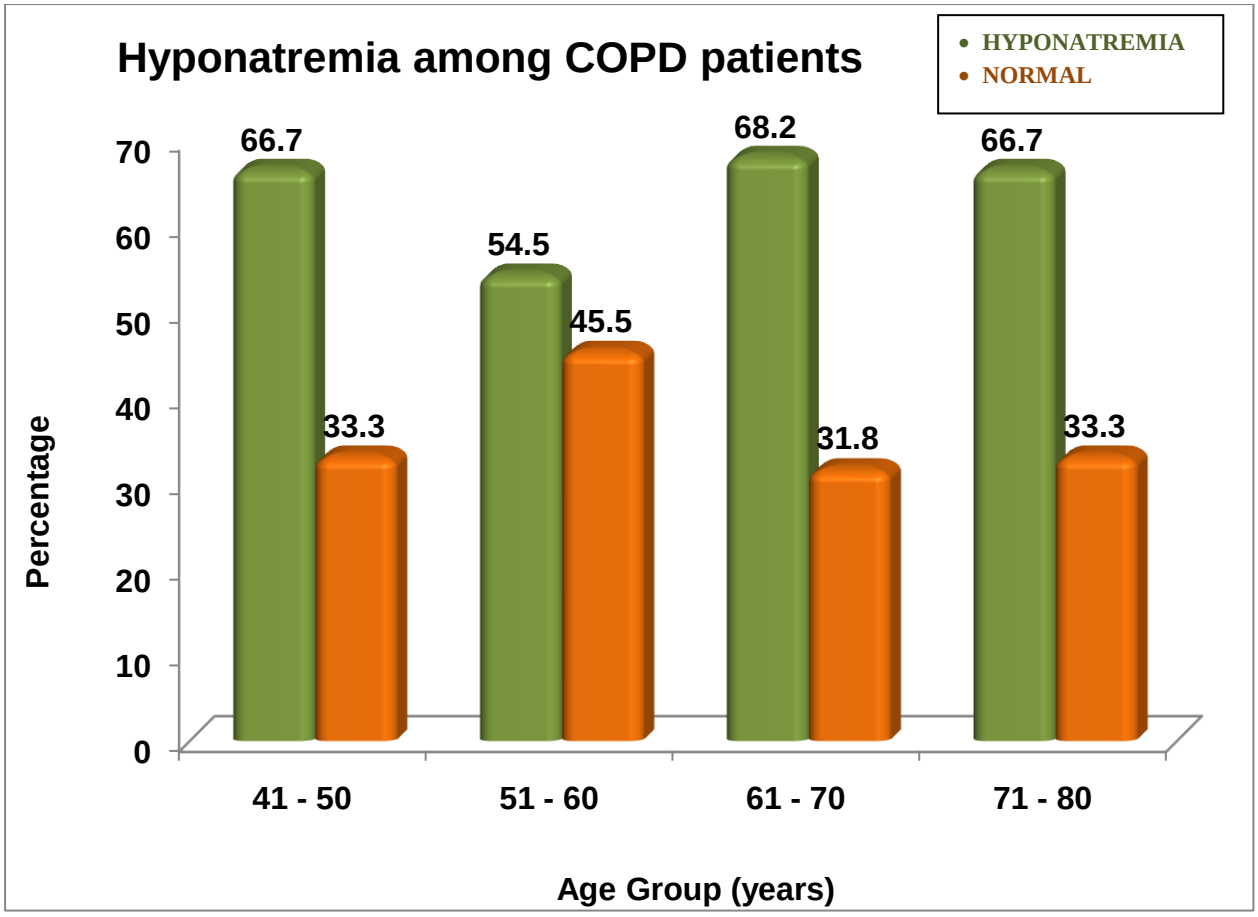
Total no. of female COPD patients - 10.

No. of female COPD patients with hyponatremia - 5.

HYPONATREMIA AMONG COPD PATIENTS – AGEWISE DISTRIBUTION:

		Sodium (Hyponatremia)				**Total**		**P-Value**
		< 135		**≥ 135**				
		N	**%**	**N**	**%**	**N**	**%**	
Age group	**41 - 50**	6	66.7	3	33.3	9	100.0	0.864
	51 - 60	12	54.5	10	45.5	22	100.0	
	61 - 70	15	68.2	7	31.8	22	100.0	
	71 - 80	2	66.7	1	33.3	3	100.0	
Total		35	62.5	21	37.5	56	100.0	

TABLE 21: HYPONATREMIA AMONG COPD PATIENTS – AGEWISE DISTRIBUTION



GRAPH 6: AGEWISE DISTRIBUTION OF HYPONATREMIA AMONG COPD PATIENTS

The incidence of renal failure among COPD patients was 42.6% as compared to 16.1% among the control population in our study.

Similar results were obtained in the study Chronic Renal Failure - a neglected comorbidity of COPD conducted by **R A Incalzi** and others [44].In this study the incidence of renal failure among the COPD patients was 43% as compared to 23.4% among controls.

AUTHOR	RENAL FAILURE IN COPD PATIENTS	RENAL FAILURE IN CONTROL GROUP
R A Incalzi	43 %	23.4%
Present study	42.6%	16.1%

TABLE 22: COMPARISON OF VARIOUS STUDIES WITH RESPECT TO RENAL FAILURE IN COPD PATIENTS

In a study Association between COPD and CKD conducted by **Van Gestel** and others [45] in a cohort of 3358 vascular surgery patients the authors found that the prevalence of COPD was inversely related to kidney function. COPD was present in 47, 38 and 32% of patients with an estimated GFR <60, 60–89 and ≥90 mL/min/1.73 m2, respectively. COPD was independently associated with CKD. Besides moderate and severe COPD were associated with increased long-term mortality in patients with CKD compared to patients without COPD.

SUMMARY

Renal failure was more prevalent among COPD patients (42.6%) when compared with age and sex matched control population (16.1%).this association was statistically significant (p=0.003).

Hyponatremia was more prevalent among COPD patients (62.5%) when compared with control group (9.3%).this association was statistically significant($p = 0.001$).

Anemia and hypoalbuminemia were more prevalent among the COPD patients when compared with controls but the association was not statistically significant.

The severity of renal failure correlated with the severity of hyponatremia.

As the renal function i.e. the creatinine clearance decreased the magnitude of decline in serum sodium also increased. This correlation was statistically significant with a p value of 0.005.

CONCLUSION

COPD is the seventh most common chronic disease and is expected to rank fourth by the year 2020.It is the fourth most common cause of death in the world. It is estimated that every year half a million people die due to COPD in our country. The mortality due to COPD is expected to increase in the future.

COPD is associated with several other comorbid illnesses like coronary artery disease, musculoskeletal diseases, malignancy because of the common risk factors involved. The association of COPD with renal failure was only recently recognized. The extent of association of COPD with renal failure has been analysed in a few studies in the western population.

The reason for not recognizing the association of renal failure with COPD could be due to the reduced muscle mass in COPD patients leading to a normal serum creatinine despite significant decline in renal function. This is termed as concealed renal failure. This implies that whenever possible in COPD patients the GFR should be estimated by calculating the estimated creatinine clearance using standard formulas like the MDRD formula which have been validated in large scale studies. Serum creatinine alone would not be an ideal marker of renal function in these patients.

We excluded COPD patients with other comorbid illness which might affect renal function. In our study we found that a significant proportion of patients with COPD had renal failure when compared with age and sex matched control population. This has therapeutic implications such as modifying the drug dosage to prevent toxicity. It is proposed that COPD induces systemic inflammation and endothelial dysfunction which could be the cause for increased cardiovascular mortality and renal disease.

Hyponatremia was demonstrated in a significant proportion of COPD patients as compared with the control population. In many diseases such as decompensated chronic liver diseases, congestive heart failure etc. hyponatremia has been found to be a significant predictor of prognosis indicating the severity of underlying disease. In our study we found that serum sodium had a positive correlation with creatinine clearance i.e. with decreasing levels of creatinine clearance there was more severe hyponatremia. Thus hyponatremia, renal failure and its magnitude can be an important prognostic tool in patients with COPD as well. This hypothesis has to be tested in future studies.

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PROFORMA

- NAME : SL. NO:
- AGE /SEX:
- ADDRESS WITH CONTACT NUMBER:
- IP NO:
- DATE OF ADMISSION:
- DATE OF DISCHARGE:

HISTORY OF PRESENTING ILLNESS:

COUGH WITH EXPECTORATION

SPUTUM

CHARACTER

QUANTITY

BREATHLESSNESS

FEVER

LEG SWELLING

DECREASED URINE OUTPUT

PAST HISTORY:

WHETHER A KNOWN CASE OF DM/HYPERTENSION/ASTHMA/TB/EPILEPSY/CARDIAC ILLNESS/ RENAL DISORDER

H/O SIMILAR EPISODES IN THE PAST, IF ANY:

H/O MAJOR ILLNESS/ HOSPITAL ADMISSIONS, IF ANY

PERSONAL HISTORY:

SMOKING HISTORY:

NO. OF PACKS / DAY:

NO. OF YEARS:

ALCOHOL CONSUMPTION

TREATMENT HISTORY:

CLINICAL EXAMINATION:

GENERAL EXAMINATION:

SYSTEMIC EXAMINATION:

CVS

RS

PER ABDOMEN

CNS

CLINICAL DIAGNOSIS:

INVESTIGATIONS:

- XRAY CHEST
- SPUTUM – FOR SMEAR EXAMINATION (GRAM STAIN, AFB STAIN,SMEAR FOR FUNGUS)
- SPUTUM FOR CULTURE AND ANTIBIOTIC SENSITIVITY
- ABG ANALYSIS (WHEN INDICATED),
- RFT WITH ELECTROLYTES
- BASIC INVESTIGATIONS(CBC, LFT, URINE ROUTINE, ECG)
- USG ABDOMEN
- ECHOCARDIOGRAM

- OTHER INVESTIGATIONS(TAILORED FOR EACH PATIENT):

FOLLOW UP:

S NO	NAME	AGE	SEX	Hb	ALBUMIN	UREA
1	RAGHURAMAN	54	M	14	4.5	18
2	PACHAIAPPAN	60	M	8	3	39
3	KOTHANDAM	65	M	15	4	17
4	GOPAL	64	M	6.9	3.4	42
5	AMUDHAN	66	M	8.5	3.2	30
6	PERUMAL	58	M	15	4	40
7	RAMAIAH	60	M	15	4	18
8	VENUGOPAL	60	M	7.4	5.2	40
9	SENGAN	53	M	6.9	3.4	48
10	KATHIRVEL	50	M	10.4	4.9	50
11	MARIAPPAN	41	M	10.1	2.9	40
12	SADASIVAM	62	M	13.7	4.2	24
13	AMUDHAN	62	M	15	4	16
14	JAYARAM	62	M	7.9	2.7	70
15	MUNUSAMY	58	M	13.6	3.1	38
16	SAMBANDAMOORTHY	56	M	14	4.5	38
17	RAJA	60	M	13.7	4.2	24
18	RAMAIAH	65	M	14	4.5	16
19	MURUGESAN	70	M	11.8	3.4	33
20	KANNIAPPAN	63	M	14.6	3.8	42
21	THOMBARAI	65	M	10.8	3.2	29
22	DHARMALINGAM	67	M	8.3	3.2	70
23	SUBRAMANI	50	M	14	4.5	17
24	SANDANAM	60	M	13.7	4.2	17
25	SUBRAMANI	70	M	14	3.3	26
26	RAMALINGAM	62	M	15.2	4.5	16
27	VELUSAMY	73	M	15	4.6	52
28	SANDEEP	55	M	8.8	4	48
29	JAYARAJ	56	M	15	3.9	40
30	KUMAR	52	M	13.7	4	20
31	JAYARAMAN	60	M	7.5	4.2	52
32	MUTHU	50	M	14.3	3.1	66
33	RAJAN	55	M	14.7	3.9	72
34	KUMAR	48	M	14.3	4.2	36
35	MURUGESAN	62	M	15	4.5	40
36	NAGARAJ	65	M	14	4	39
37	PETER	64	M	15	4.6	40
38	RAMESH	60	M	5.8	5.1	40
39	IBRAHIM	52	M	9.7	3.7	48
40	ABDULLA	58	M	6.6	4.2	50
41	VALLI	46	F	13.7	4.4	62
42	RAJESHWARI	52	F	10.6	3.9	30
43	KUMARI	49	F	14.3	4	40
44	LAKSHMI	68	F	12.6	3.8	38
45	MARI	54	F	10.3	4	37
46	KANNAMMA	49	F	7.3	3.9	72
47	CHANDRAMMA	62	F	14.3	4	42
48	MASTHANBEEVI	72	F	12.5	3.7	56
49	NOORJAHAN	68	F	7.2	3.9	54

50	MARY	68	F	6.4	5	62
51	RAJAN	52	M	13.5	4.4	42
52	SANTHANAM	49	M	15	4	46
53	IRUDAYARAJ	66	M	14	4.5	45
54	KUMAR	64	M	15	4	44
55	JOSEPH	72	M	14.3	3.9	26
56	MANI	54	M	14	4.5	32

CREATININE	SODIUM	POTASSIUM	CREATININE CLEARANCE
0.8	139.1	3.62	107.1
1.3	131.7	3.36	59.8
0.8	123	3.2	103.1
1.4	123.9	3.25	54.2
1.3	116.4	3.62	58.7
0.8	132	3.8	105.5
0.9	126.1	3.35	91.5
1.5	133.7	2.49	50.7
1.6	117.8	3.54	48.3
1.6	132	3.49	48.9
1.5	130.8	4.07	54.8
1	136.1	3.63	80.5
0.8	141.4	4.75	104.1
2.1	110	4.2	34.2
1.2	135	3.02	66.1
0.9	136	4	92.8
1	130.4	3	81
0.8	129.4	3.05	103.1
0.8	132	3.86	101.6
1.5	128.8	3.74	50.2
1	125.1	2.6	80
2.8	132	3.21	24
0.9	116.4	3.53	95
0.9	131.1	4.21	91
1.1	123.5	3.53	70
0.8	122.7	4.21	104
1.4	132	3.2	53
0.8	135	3	107
1.2	131	4.2	67
0.8	128	5	108
1.6	130	4	47
1.5	135	4	53
1.8	136	3.2	42
0.8	129.4	3.4	110
0.6	136	4	145
1.3	131.7	3.36	59
0.8	132	3.8	103
1.5	133.7	4.29	51
1.6	117.8	3.54	48
1.6	136	3.72	47
1.4	130	3.64	43
0.8	138	4	80
0.9	142	3.86	71
1	139	4.82	59
0.8	140.8	4.12	79
1.8	128	5	32
0.6	144.4	5	108
1.3	132	3.96	43
1.4	131.4	4.6	40

1.6	130.9	4.12	34
0.8	135.2	3.82	112
0.9	138.9	4.06	95
0.7	140.6	3.65	120
0.7	140.4	4.15	121
0.8	142.8	5	101
0.6	145.1	3.8	149

S NO	NAME	AGE	SEX	Hb	ALBUMIN	UREA
1	RAGHURAMAN	54	M	14	4.5	18
2	PACHAIAPPAN	60	M	8	3	39
3	KOTHANDAM	65	M	15	4	17
4	GOPAL	64	M	6.9	3.4	42
5	AMUDHAN	66	M	8.5	3.2	30
6	PERUMAL	58	M	15	4	40
7	RAMAIAH	60	M	15	4	18
8	VENUGOPAL	60	M	7.4	5.2	40
9	SENGAN	53	M	6.9	3.4	48
10	KATHIRVEL	50	M	10.4	4.9	50
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13	AMUDHAN	62	M	15	4	16
14	JAYARAM	62	M	7.9	2.7	70
15	MUNUSAMY	58	M	13.6	3.1	38
16	SAMBANDAMOORTHY	56	M	14	4.5	38
17	RAJA	60	M	13.7	4.2	24
18	RAMAIAH	65	M	14	4.5	16
19	MURUGESAN	70	M	11.8	3.4	33
20	KANNIAPPAN	63	M	14.6	3.8	42
21	THOMBARAI	65	M	10.8	3.2	29
22	DHARMALINGAM	67	M	8.3	3.2	70
23	SUBRAMANI	50	M	14	4.5	17
24	SANDANAM	60	M	13.7	4.2	17
25	SUBRAMANI	70	M	14	3.3	26
26	RAMALINGAM	62	M	15.2	4.5	16
27	VELUSAMY	73	M	15	4.6	52
28	SANDEEP	55	M	8.8	4	48
29	JAYARAJ	56	M	15	3.9	40
30	KUMAR	52	M	13.7	4	20
31	JAYARAMAN	60	M	7.5	4.2	52
32	MUTHU	50	M	14.3	3.1	66
33	RAJAN	55	M	14.7	3.9	72
34	KUMAR	48	M	14.3	4.2	36
35	MURUGESAN	62	M	15	4.5	40
36	NAGARAJ	65	M	14	4	39
37	PETER	64	M	15	4.6	40
38	RAMESH	60	M	5.8	5.1	40
39	IBRAHIM	52	M	9.7	3.7	48
40	ABDULLA	58	M	6.6	4.2	50
41	VALLI	46	F	13.7	4.4	62
42	RAJESHWARI	52	F	10.6	3.9	30
43	KUMARI	49	F	14.3	4	40
44	LAKSHMI	68	F	12.6	3.8	38
45	MARI	54	F	10.3	4	37
46	KANNAMMA	49	F	7.3	3.9	72
47	CHANDRAMMA	62	F	14.3	4	42
48	MASTHANBEEVI	72	F	12.5	3.7	56
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50	MARY	68	F	6.4	5	62
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52	SANTHANAM	49	M	15	4	46
53	IRUDAYARAJ	66	M	14	4.5	45
54	KUMAR	64	M	15	4	44
55	JOSEPH	72	M	14.3	3.9	26
56	MANI	54	M	14	4.5	32

CREATININE	SODIUM	POTASSIUM	CREATININE CLEARANCE
0.8	139.1	3.62	107.1
1.3	131.7	3.36	59.8
0.8	123	3.2	103.1
1.4	123.9	3.25	54.2
1.3	116.4	3.62	58.7
0.8	132	3.8	105.5
0.9	126.1	3.35	91.5
1.5	133.7	2.49	50.7
1.6	117.8	3.54	48.3
1.6	132	3.49	48.9
1.5	130.8	4.07	54.8
1	136.1	3.63	80.5
0.8	141.4	4.75	104.1
2.1	110	4.2	34.2
1.2	135	3.02	66.1
0.9	136	4	92.8
1	130.4	3	81
0.8	129.4	3.05	103.1
0.8	132	3.86	101.6
1.5	128.8	3.74	50.2
1	125.1	2.6	80
2.8	132	3.21	24
0.9	116.4	3.53	95
0.9	131.1	4.21	91
1.1	123.5	3.53	70
0.8	122.7	4.21	104
1.4	132	3.2	53
0.8	135	3	107
1.2	131	4.2	67
0.8	128	5	108
1.6	130	4	47
1.5	135	4	53
1.8	136	3.2	42
0.8	129.4	3.4	110
0.6	136	4	145
1.3	131.7	3.36	59
0.8	132	3.8	103
1.5	133.7	4.29	51
1.6	117.8	3.54	48
1.6	136	3.72	47
1.4	130	3.64	43
0.8	138	4	80
0.9	142	3.86	71
1	139	4.82	59
0.8	140.8	4.12	79
1.8	128	5	32
0.6	144.4	5	108
1.3	132	3.96	43
1.4	131.4	4.6	40

1.6	130.9	4.12	34
0.8	135.2	3.82	112
0.9	138.9	4.06	95
0.7	140.6	3.65	120
0.7	140.4	4.15	121
0.8	142.8	5	101
0.6	145.1	3.8	149

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : A Study on renal Dysfunction in COPD patients

Principal Investigator : Dr. N. Idhayachandran

Designation : PG in M.D (Gen.Med.)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-1

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 11.06.2012 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு

"சி.ஓ.பி.டி. நோயாளிகளுக்கு ஏற்படும் சிறுநீரக பாதிப்புகள்"

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்லி மருத்துவமனை
சென்னை - 600 001.

பங்கு பெறும் நோயாளியின் பெயர் : வயது :

பங்கு பெறும் நோயாளியின் எண் : பாலினம் : ஆண் ☐ பெண் ☐

நோயாளியின் விலாசம் :

நோயாளி இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிடப்பட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும். அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் என்னை இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்க அனுமதிக்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என்னை இவ்வாய்வில் இருந்து விலக்கி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். என்னை ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்த கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணிக்கு தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

நோயாளியின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை (இந்த படிவம் படித்து காட்டப்பட்டு புரிந்து கைரேகை அளிக்கின்றேன்)

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

.....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....